OPTIMIZATION OF TECHNOLOGICAL PARAMETERS BY ACOUSTIC CAVITATION TO ACHIEVE PARTICLE SIZE REDUCTION

CSILLA BARTOS, PIROSKA SZABÓ-RÉVÉSZ, RITA AMBRUS*

Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6, H-6725 Szeged, Hungary
**Corresponding author: arita@pharm.u-szeged.hu*

Abstract

This article reports on particle engineering by a top-down method involving the organic solvent-free acoustic cavitation of ibuprofen (IBU). The process parameters (temperature, amplitude, sonication period and stabilizers) were optimized. The particle size distribution of IBU was measured after sonication and compared with the raw IBU (D 0.5=153 μm). Due to acoustic cavitation, the particle size decreased (D 0.5=25 μm), but the use of a stabilizer was needed for further decrease (D 0.5=11 μm). Samples sonicated with optimized process parameters, containing the most efficient stabilizer, were dried, their morphology was characterized by scanning electron microscopy and the structure was determined by differential scanning calorimetery and X-ray powder diffraction (XRPD). During the thermoanalytical and XRPD characterization, the crystalline structure of IBU was detected after the sonication procedure.

Rezumat

Prezentul articol se încadrează în domeniul ingineriei particulelor prezentând o metodă de cavitare acustică fără solvent organic a ibuprofenului (IBU). Parametrii procedeului (temperatură, amplitudine, timp de sonicare şi stabilizatori) au fost optimizaţi. După sonicare s-a măsurat distribuţia mărimii particulelor de IBU. Datorită cavitării acustice, dimensiunea particulelor a scăzut (D = 0.5=25 μm), dar a fost necesară utilizarea unui stabilizator pentru o scădere mai pronunţată (D 0.5=11 μm). Probele sonicate, cu parametrii de proces optimizaţi, conţinând cel mai eficient stabilizator, au fost uscate şi caracterizate morfologic prin microscopie de scanare electronică, precum şi structural, prin calorimetrie de scanare diferenţială şi difracţie de raze X (XRPD). În timpul analizei termice şi XRPD, structura cristalină a IBU a fost identificată după sonicare.

Keywords: Acoustic cavitation, Particle engineering, Particle size reduction

Introduction

Particle engineering techniques have been developed to produce drug particles with modified physico-chemical and biopharmaceutical properties. Different procedures are employed in order to optimize the habit of the particles [17, 15, 21]. The procedures involve either particle size reduction of larger crystals (top-down approach - disintegration) or the building-up of particles (bottom-up approach-integration) [4, 5, 3, 2].

Energy input may be important for the particle size reduction of active substances, and is possible by cavitation [20]. Cavitation is the formation and immediate implosion of cavities in a liquid. Cavitation is usually divided into two classes: inertial and non-inertial cavitation. Inertial cavitation is the process where a void or bubble in a liquid rapidly collapses, producing a shock wave. Non-inertial cavitation is the process in which a bubble in a fluid is forced to oscillate in size or shape due to some form of energy input. In pharmaceutical technology, hydrodynamic (high-pressure homogenization) and acoustic (power ultrasound) cavitation, are generally used, which are of non-inertial cavitation type. Acoustic cavitation, a novel possibility to decrease particle size [2, 8, 22], has the ability to erode and break down particles [13]. Particle engineering uses ultrasound power in the frequency range 20-100 kHz to induce particle size reduction [23].

Power ultrasound is used for the processing of liquids, e. g. mixing, emulsifying, dispersing and de-agglomeration or milling. During sonication, the sound waves that propagate into the liquid media result in alternating high-pressure and low-pressure cycles, with rates depending on the frequency. During the low-pressure cycle, high-intensity ultrasonic waves create small vacuum bubbles or voids in the liquid. If the acoustic intensity is sufficiently high, the bubbles will first grow in size and then rapidly collapse during a high-pressure cycle. This phenomenon is termed ultrasonic cavitation [24]. Ultrasonic liquid processing is described by a number of parameters (amplitude, pressure, temperature and concentrations of compounds). The effect of the process may be determined as a function of the energy *per* processed volume:

$$\text{effect} = f\,(E/V)$$

where the energy (E) is the product of the power output (P) and the duration of exposure (t):

$$E[Ws] = P[W] * t[s]$$

The function alters with changes in the individual parameters. Additionally, the actual power output *per* surface area of the sonotrode of an ultrasonic unit depends on the parameters [10].

Ibuprofen is a non-steroidal anti-inflammatory drug, which is often used for the relief of symptoms of arthritis or fever, and as an analgesic [26, 16]. We chose IBU as a model crystalline drug because of its large particle size (D 0.5=153.73 μm) and low melting point (approximately 75 °C) [12]. Formulation of the IBU-β-cyclodextrin complex [6] and amorphization of this drug are known as feasible ways to increase its solubility [25]. The rapid expansion of supercritical solutions (supercritical fluid technology)

[11, 19], melt emulsification [14] and the solvent diffusion method [12] are well known to decrease the particle size of IBU through use of an organic solvent, but the residual organic solvent may be a problem in the pharmaceutical formulation.

In the present work, the use of acoustic cavitation, as a novel organic solvent-free, static wet grinding technique in pharmaceutical technology is reported. The aims of our work were to reduce the particle size of IBU to the micrometer range by using power ultrasound, with optimization of the process parameters (temperature, amplitude and sonication period) and excipients, and to study the effects of power ultrasound on the physico-chemical properties of IBU.

Materials and Methods

Materials

IBU 2-[4-(2-methylpropyl)phenyl]propanoic acid, was purchased from Aldrich Chemie, Deisenhofen, Germany; PVP K-25 (polyvinylpyrrolidone) was purchased from ISP Customer Service GmBH, Köln, Germany; Poloxamer 188 (polyethylene-polypropylene-glycol) was from BASF, Ludwigshafen, Germany; Tween 80 (Polysorbat 80; polyoxyethylenesorbitan-monooleate) was from Hungaropharma, Budapest, Hungary; and Solutol HS 15 (polyethylene glycol 15-hydroxystearate) was from BASF, Ludwigshafen, Germany.

Methods

Optimization of process parameters

A power ultrasound device (Hielscher UP 200S Ultrasonic processor with 200 W, Germany) was applied for energy input in the sample preparation. The samples (suspensions containing 300 mg of pure IBU in 30 mL of water) were sonicated at room temperature without cooling (the initial suspension temperature was 25°C) and using an ice bath with standardized temperature at around 18°C (the initial suspension temperature was 18°C, the temperature of the cooling water was monitored continuously). A range of ultrasonic amplitudes (30%, 50% and 70%) were tested in order to determine the optimum amplitude *via* a 200 W model ultrasound device for 10, 20 or 30 min during the procedures (Table I) (Figure 1).

Table I
Parameters applied during sonication

Temperature (°C)	room temperature, ice cooling
Amplitude (%)	30, 50, 70
Time (min)	10, 20, 30

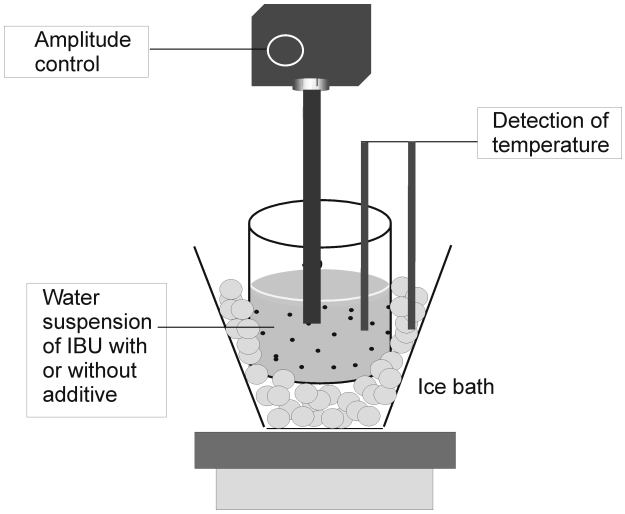


Figure 1
Scheme of preparation

Effects of stabilizers on particle size distribution

During the content optimization, different additives were applied: PVP K-25, Poloxamer 188, Tween 80 and Solutol HS 15. PVP K-25 is a stabilizer, Poloxamer 188 is a non-ionic surfactant, Tween 80 is an emulsifier and solubilizer, and Solutol HS 15 is a non-ionic solubilizer. These may promote particle size reduction and prevent agglomeration by stabilizing the particles against inter-particle forces [9, 8]. When the influence of these stabilizers was investigated, the stabilizer was dissolved in water and a fixed concentration of IBU was suspended in an aqueous solution of the excipient. The effects of the concentration of IBU (1 and 0.25 m/v %) on the particle size decrease were also studied (Table II). The concentrations of the stabilizers were determined as in previous studies: 0.5 and 0.25 m/v % of excipients were tested [12].

Table II
Applied additives, concentration of IBU and additives

Additives	PVP K-25, Poloxamer 188, Tween 80, Solutol HS 15
Concentration (m/v %)	1, 0.25 (IBU) 0.5, 0.25 (additive)

Preparation of solid products

Suspensions prepared with the optimized parameters with efficient stabilizer were dried in a static bed dryer (Memmert, Germany) at 50 °C in order to obtain solid products. 50 °C was chosen because of the low melting point of IBU, which could fuse at higher temperature. The yield of IBU was approximately 90%. After drying, the physico-chemical properties of the products were investigated.

Particle size distribution and morphology

The volume particle size distribution of raw IBU was measured by laser diffraction (Mastersizer 2000, Malvern Instruments Ltd, Worcestershire, UK) with the following parameters: 300RF lens; small volume dispersion unit (3000 rpm); refractive index for dispersed particles 1.4364; refractive index for dispersion medium 1.330. Water was used as dispersant and the obscuration was in the range 11-16% for each measurement. The IBU particle size was determined immediately on the initial water suspension. After drying, the solid product was resuspended in water using an ultrasonic bath for 5 min. Water was applied as dispersion phase, in which the additives were dissolved, and therefore only IBU particles could be detected. In all cases the average size volume distribution, D 0.1, D 0.5, and D 0.9 were determined and evaluated.

The shape and surface characteristics of the various samples were visualized by using a scanning electron microscope (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan). Briefly, the samples were sputter-coated with gold–palladium under an argon atmosphere, using a gold sputter module in a high-vacuum evaporator and the samples were examined at 15 kV and 10 μA. The air pressure was 1.3-13.0 mPa.

Structural analysis

DSC measurements were carried out with a Mettler Toledo DSC 821^e thermal analysis system with the STAR^e thermal analysis program V9.0 (Mettler Inc., Schwerzenbach, Switzerland). Approximately 2-5 mg of pure drug or product was examined in the temperature range between 25 °C and 300 °C. The heating rate was 5 °C min^{-1}. Argon was used as carrier gas at a flow rate of 10 L h^{-1} during the DSC investigations.

The physical state of IBU in the samples was evaluated by X-ray powder diffraction (XRPD). XRPD patterns were produced with an X-ray Diffractometer Miniflex II (Rigaku Co. Tokyo, Japan), where the tube anode was Cu with K_α = 1.5405 Å. The pattern was collected with a tube

voltage of 30 kV and a tube current of 15 mA in step scan mode (4° min^{-1}). The instrument was calibrated by using Si.

Results and Discussion

Effects of process parameters on particle size distribution

During the procedure, the experimental parameters were first investigated. The amplitude, temperature and sonication time were varied (Table III). In the starting suspensions, the concentration of IBU (with an average particle size of about 154 μm) was 300 mg in 30 mL of water. For each sample, three parallel measurements were performed to check the reproducibility.

At room temperature, the application of an amplitude of 30, 50 or 70% resulted in a 50% decrease in the average IBU particle size. During the procedure, the temperature of the suspension increased from 25 °C to 77-85 °C. We presumed that some of the invested energy was transformed to heat, and the D 0.9 value was therefore increased by amplitudes of 30 and 50% (Sample 1 and Sample 2) relative to raw IBU (Figure 2 on the left). The reason for these phenomena is the melting of IBU, due to the temperature of the system increasing to above the melting point of IBU (75°C). After the impaction, therefore, the sample presented large precipitated IBU crystals.

For Samples 4-6, continuous ice cooling ($T_{cooling\ water}$ = 18 °C) was applied. After the procedure, the temperature of the suspension was decreased to approximately 35 °C, which prevented the melting of IBU. Furthermore, the cohesive forces (which promote the aggregation of the particles) were lower at low temperature, and this helped achieve smaller particles. Sonication with an amplitude of 30% caused a further 50% decrease in the average particle size. The smallest particles were produced by the application of an amplitude of 70%, with the largest energy investment, on use of an ice bath (Sample 6).

Increase of the amplitude of sonication did not cause a significant alteration in the temperatures of the suspensions relative to one another at 18 °C on ice cooling. Increasing of the duration of sonication to 20 min resulted in a lower size reduction than with a combination of increased amplitude and cooling (Figure 2). No difference in particle size was observed when the sonication time was increased from 20 min to 30 min. A sonication time of 20 min was therefore, considered to be optimum (Sample 7 and Sample 8).

Consequently, the increased amplitude-due to the largest energy investment and decreased temperature-due to lower cohesive forces and less energy-transformation to heat-jointly resulted in the most effective particle size reduction; the best combination was sonication with an amplitude of 70% for 20 min with ice cooling, which resulted in an average IBU particle size of more than 25 μm because of grinding resistance (Figure 2).

The use of a lower concentration of active substance might be predicted to yield a smaller particle size after the sonication, energy is directed to less material and the cohesive forces are weaker. Decrease of the concentration of IBU (0.25 m/v%) did not cause a further particle size reduction (Sample 9) as compared with the results at a higher concentration of IBU (Figure 2), which allows formulation with a larger quantity of active substance.

Table III

Effects of acoustic cavitation on particle size distribution at different parameters

Batch code	Investi-gated factor	Amp-litude %	Starting temperature of suspension (°C)	Temperature of suspension after sonication (°C)	Time (min)	Conc. of IBU (mg/30 mL water)	Particle size distribution (μm) D 0.5
Raw IBU		-------	-------	-------	-------	-------	153.73
Sample 1		30	25	77.7	10	300	85.16±9.14
Sample 2	Amp.	50	25	73.7	10	300	85.35±3.85
Sample 3		70	25	85.0	10	300	84.49±1.63
Sample 4		30	18	32.3	10	300	39.44±2.10
Sample 5	Temp.	50	18	34.5	10	300	31.92±2.63
Sample 6		70	18	40.0	10	300	28.19±2.30
Sample 6		70	18	40.0	10	300	28.19±2.30
Sample 7	Time	70	18	40.0	20	300	25.78±2.20
Sample 8		70	18	37.6	30	300	24.88±2.87
Sample 7		70	18	40.0	20	300	25.78±2.20
Sample 9	Conc.	70	18	37.8	20	75	22.24±5.82

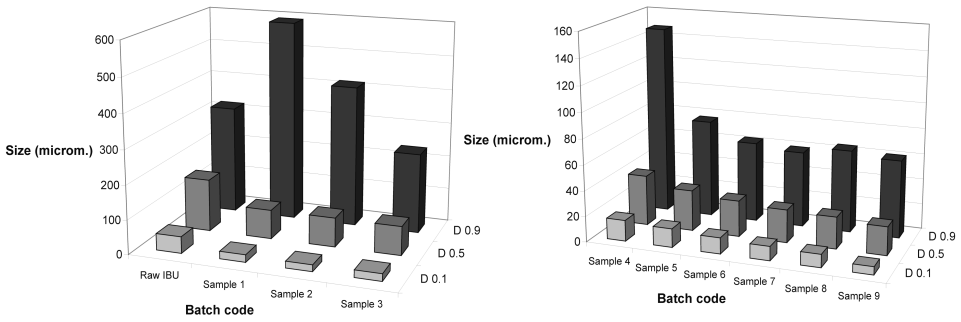


Figure 2
Particle size distribution of IBU after sonication under different conditions (Samples 1-9)

Effect of stabilizers

The choice of stabilizer is specific for each drug candidate and each formulation procedure. The stabilizer should exhibit sufficient affinity for the particle surface in order to stabilize the suspension. When the influence of different stabilizers was investigated, the suspensions were prepared with a fixed concentration of the drug and optimized parameters (see Sample 7). The type of compound employed for stabilization has a pronounced effect on the particle size and distribution (Table IV). Four different stabilizers were tested to check the effect of the nature of the surfactant on the IBU particle size. Micronized drugs have a tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area [8, 1]. One of the most common methods to reduce the tendency to drug agglomeration is a steric technique. Steric stabilization is achieved by adsorbing polymers onto the drug particle surface [9], forming a protective layer on the surface of the particles and overcoming the cohesive forces. Solutol was least effective, followed by PVP and Tween 80. The smallest particle size was achieved with Poloxamer: the average size was approximately 11 μm. When Poloxamer was used, this stabilizer exerted a strong steric stabilization effect preventing aggregation of the particles. An important function of polymers (e. g. Poloxamer) is that they can form a substantial mechanical and thermodynamic barrier at the interface, which retards the approach and coalescence of individual emulsion droplets [7]. Non-ionic non-polymeric surfactants (e.g. Tween) offer an advantage over polymers in that they have a higher adsorption potential than an equal-chain-length polymer [18].

The use of a lower concentration of Poloxamer might be expected to lead to a large IBU particle size because it could well be less effective as

regards overcoming the cohesive forces. However, a decreased concentration of Poloxamer did not cause a particle size reduction: no significant change in average particle size occurred.

Table IV

Effects of additives on IBU particle size distribution

Sample	Type of additive	Size		
		D 0.1 (μm)	D 0.5 (μm)	D 0.9 (μm)
Sample 7	-------	10.97±1.65	25.78±2.20	59.18±1.73
Sample 10	0.5% PVP	5.82±0.08	12.56±0.11	24.55±1.09
Sample 11	0.5% Tween	5.29±0.03	11.14±0.11	23.64±2.33
Sample 12	0.5% Solutol	6.71±0.11	14.57±0.28	27.74±0.63
Sample 13	0.5% Polox	5.13±0.23	11.09±0.03	21.47±0.62
Sample 14	0.25% Polox	5.26±0.43	11.53±0.40	22.49±0.23

Table V lists the optimum experimental factors for the most efficient IBU particle size reduction. The batch containing 0.25% Poloxamer as stabilizer and sonicated with an amplitude of 70% for 20 min under ice cooling was dried in a static bed dryer at 50 °C in order to obtain a solid product.

Table V

Sample produced with optimized parameters using the most appropriate additive

	Additive	Amp/T (%)/(°)	T (Susp) (°)	Time (min)	Conc. (mg/30 mL)	Size D 0.5 (μm)
Dried Sample 14	0.25% Polox.	70/ 18	35.5	20	300	11.5

Characterization of dried product

Particle size distribution and morphology

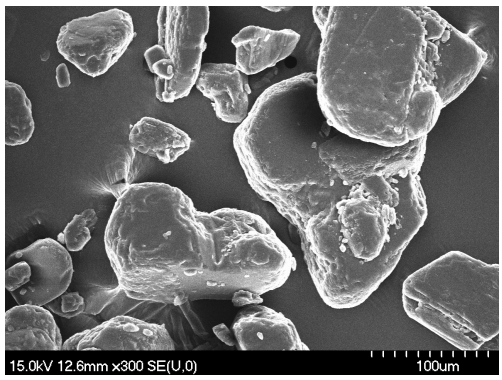
The change in average particle size on drying was not significant as compared with the suspension of Sample 14: aggregation did not occur. The specific surface area of IBU increased 10-fold due to acoustic cavitation and was not altered after drying (Table VI).

Table VI

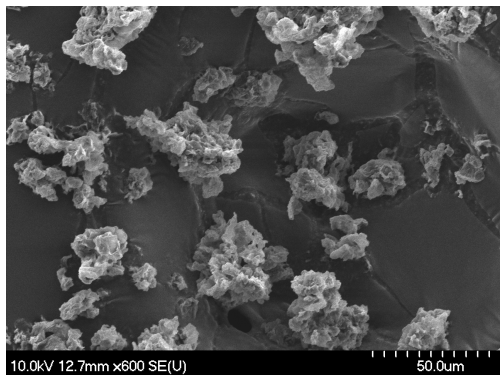
Specific surface and size distribution of pure IBU and two samples

	Spec. surface (m^2/g)	D 0.1 (μm)	D 0.5 (μm)	D 0.9 (μm)
Raw IBU	0.062	48.50	153.73	319.36
Sample 14 (suspension)	0.598	5.26	11.53	22.49
Dried Sample 14	0.614	5.52	12.44	25.38

The SEM pictures (Figure 3) provided an indication of the morphology of the modified particles. The crystal habit of pure IBU changed significantly. The raw IBU consisted mainly of roundish crystals with a broad focal size distribution. The dried product comprised irregular-shaped crystals with an average size of 10-15 μm. Poloxamer adsorbed strongly onto the surfaces of IBU particles *via* its poly(ethylene oxide) central block and formed a layer on the IBU surface after drying. The crystal lattice of IBU demonstrated defects and cracks, along which the crystals were disintegrated due to acoustic cavitation. These two factors accounted for the relatively rough surface.



A



B

Figure 3
SEM picture of raw IBU (A), and dried Sample 14 (B)

Structure (DSC and XRPD)

DSC was employed in order to investigate the crystallinity and the melting of IBU and Poloxamer in the pure forms and in the sonicated dried product. The DSC curve (Figure 4) of pure IBU revealed a sharp endothermic peak at 76.93^{o}C, which is its melting point, confirming its crystalline structure. Poloxamer is a semi-crystalline additive (melting point:

55.84°C). The DSC curves exhibited sharp endothermic peaks of the two materials at 72.80°C (IBU) and 42.18°C (Poloxamer), indicating that the crystallinity of the drug was retained in the product. The IBU crystals in the product melted at a lower temperature than the melting point of pure IBU. This is due to the smaller particle size of IBU and the fact that the Poloxamer melted at a lower temperature, which promoted the melting of IBU. Both components melted at lower temperature in the product compared with melting point of pure materials. Several different materials alongside each other are present such as impurity of other components, which causes the melting of substances at lower melting points.

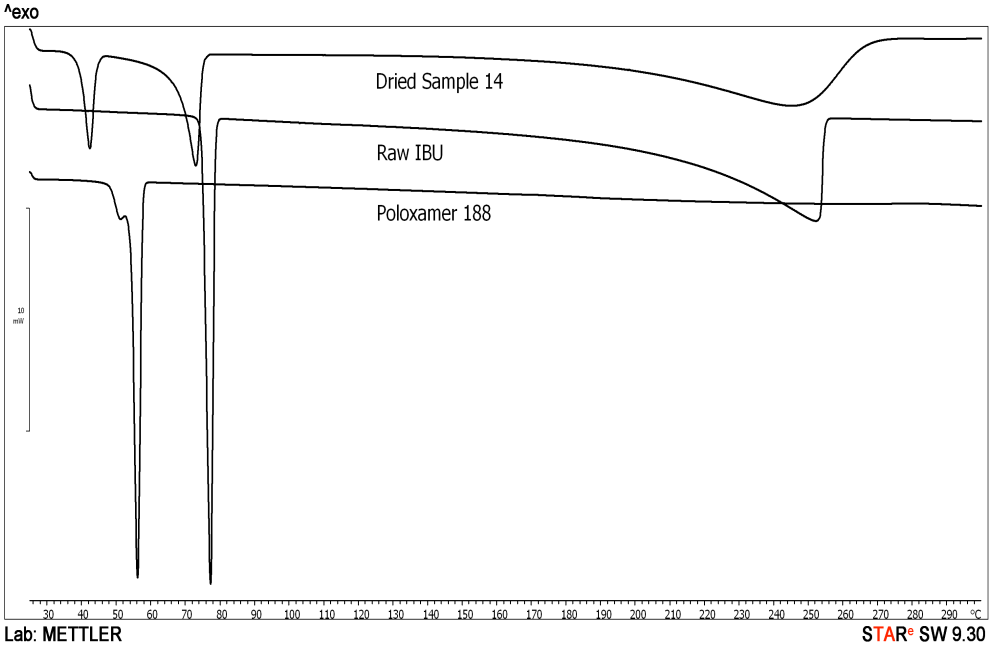


Figure 4

DSC curves of raw materials and of the product

The XRPD pattern of pure IBU demonstrated its crystalline structure, as expected. The characteristic 2θ data: 6.50, 17.00 20.20 and 22.00. The XRPD pattern of pure Poloxamer exhibited peaks at 2θ values of 19.50 and 22.00. The raw IBU and the sonicated dried IBU composite displayed similar X-ray diffraction patterns (Figure 5). This means that the crystalline form of the micronized IBU was not changed by the sonication and drying procedure.The differences in intensity of the IBU diffractogram peaks in the product as compared with raw IBU are due to the Poloxamer, a semi-crystalline additive with a crystallization inhibitory effect besides its stabilizer effect.

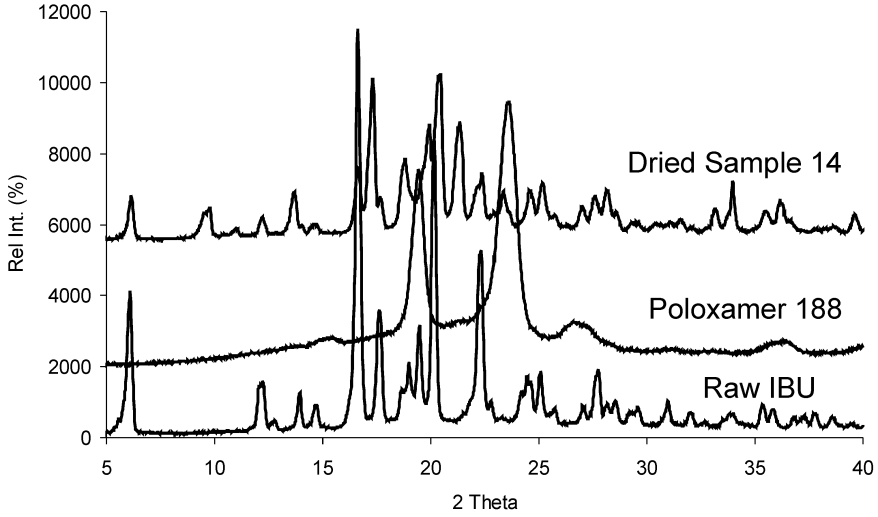


Figure 5
XRPD examination of IBU, Poloxamer and dried Sample 14

Conclusions

The top-down method can be applied to decrease the particle size and change the crystal habit, and in this way may it be useful for the formulation of original preparations and also to facilitate generic formulation.

Our study has illustrated the important role of power ultrasound in drug formulation. Because of the small amount of the samples, this method is recommended in preformulation studies. Acoustic cavitation, a static disintegration method with optimized process parameters, involving a change in crystal habit, may decrease the IBU particle size to the micrometer range. For further particle size reduction, additives are needed. The most efficient combination proved to be sonication with an amplitude of 70% for 20 min under ice cooling, with Poloxamer 188 as a stabilizer, which resulted in an average particle size of approximately 11.5 μm. The specific surface area of IBU increased 10-fold compared to the initial particle size of pure drug due to the treatment. The crystallinity of the drug was retained in the product after the sonication and drying procedure.

Wet grinding at a controlled temperature may be favourable in the grinding of materials with low melting points: the melting of the materials may be avoided.

In the future, we plan to compare static sonication with dynamic sonication in a double-walled flow cell, which allows a continuous flow of the sample during sonication.

Acknowledgements

The publication/presentation is supported by the European Union and co-funded by the European Social Fund. Project number: TÁMOP-4.2.2/B-10/1-2010-2012

Project title: "Broadening the knowledge base and supporting the long term professional sustainability of the Research University Centre of Excellence at the University of Szeged by ensuring the rising generation of excellent scientists."

References

1. Aguiar A. J., Zelmer J. E., Kinkel A. W., Deaggregation behavior of a relatively insoluble substituted benzoic acid and its sodium salt, *J. Pharm. Sci*. 1967, 56, 1243-1252.
2. Ambrus R., Amirzadi N. N., Aigner Z., Szabó-Révész P., Formulation of poorly water-soluble Gemfibrozil applying power ultrasound, *Ultrason. Sonochem*. 2012, 19, 286-291.
3. Bakar M. R. A., Nagy Z. K., Saleemi A. N., Rielly C. D., The impact of direct nucleation control on crystal size distribution in pharmaceutical crystallization processes, *Cryst. Growth and Des*. 2009, 9, 1378-1384.
4. Blagden N., M. de Matas, Gavan P. T., York P., Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, *Adv. Drug Deliver. Rev*. 2007, 59, 617-630.
5. Bund R. K., Pandit A. B., Sonocrystallization: Effect on lactose recovery and crystal habit, *Ultrason. Sonochem*. 2007, 14, 143-152.
6. Chow D. D., Karara A. H., Characterization, dissolution and bioavailability in rats of ibuprofen- β -cyclodextrin complex system, *Int. J. Pharm*. 1986, 28, 95-101.
7. D. Myers, Surfaces, Interfaces and Colloids: Principles and Applications (second ed.), in: Wiley-VCH, Weinheim, 1999, pp. 253–294.
8. Friedrich H., Fussnegger B., Kolter K., Bodmeier R., Dissolution rate improvement of poorly water-soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers, *Eur. J. Pharm. Biopharm*. 2006, 62, 171-177.
9. Ghosh I., Bose S., Vippagunta R., Harmon F., Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth, *Int. J. Pharm*. 2011, 409, 260-268.
10. Ghica MV, Albu MG, Titorencu I, Albu L, Popa L, Collagen-doxycycline topical hydrogels: rheological, kinetic and biocompatibility studies, *Farmacia*, 2012, 60(6), 866-876
11. Kayrak D., Akman U., Hortaçsu Ö., Micronization of Ibuprofen by RESS, *J. Supercrit. Fluid* 2003, 26, 17-31.
12. Kocbek P., Baumgartner S., Kristl J., Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs, *Int. J. Pharm*. 2006, 312, 179-186.
13. Kuldiloke J., Effect of Ultrasound, Temperature and Pressure Treatments on Enzyme Activity an Quality Indicators of Fruit and Vegetable Juices, Ph. D. Thesis at Technische Universität Berlin 2002; http://opus.kobv.de/tuberlin/volltexte/2002/440/pdf/kuldiloke_jarupan.pdf
14. Manish M., Harshal J., Anant P., Melt sonocrystallization of ibuprofen: Effect on crystal properties, *Eur. J. Pharm. Sci*. 2005, 25, 41-48.
15. Miclea L. M., Vlaia L., Vlaia V., Hădărugă D. I., Mircioiu C., Preparation and characterization of inclusion complexes of meloxicam and α-cyclodextrin and β-cyclodextrin, *Farmacia* 2010, 58, 5, 583-593.
16. Miles S., Ibuprofen, xPharm: The comprehensive pharmacology Reference, 2007, pp. 1-7.
17. Nandiyanto A. B. D., Okuyama K., Progress in developing spray-drying methods for the production of controlled morphology particles: From the nanometer to submicrometer size ranges, *Adv. Powder Technol*. 2011, 22, 1-19.

18. Palla B. J., Shah D. O., Stabilization of high ionic strength slurries using surfactant mixtures: molecular factors that determine optimal stability, *J. Colloid Interf. Sci*. 2002, 256, 143–152.
19. Pathak P., Meziani M. J., Desai T., Sun Y. P., Formation and stabilization of ibuprofen nanoparticles in supercritical fluid processing, *J. Supercrit. Fluid* 2006, 37, 279-286.
20. Patil M. N., Pandit A. B., Cavitation-A novel technique for making stable nano-suspensions, *Ultrason. Sonochem*. 2007, 14, 519-530.
21. Popa L, Ghica MV, Ibuprofen pediatric suspension designed and optimized by response surface methodology, *Farmacia*, 2011, 59(4), 500-506
22. Raman V., Abbas A., Experimental investigations on ultrasound mediated particle breakage, *Ultrason. Sonochem*. 2008, 15, 55-64.
23. Sandilya D. K., Kannan A., Effect of ultrasound on the solubility limit of sparingly soluble solid, *Ultrason. Sonochem*. 2010, 17, 427-434.
24. Suslick K. S., Sonochemistry, in: J. Wiley & Sons (4th Ed), Kirk-Othmer Encyclopedia of Chemical Technology, New York, 1998, pp. 517-541.
25. Szabó-Révész P., Laczkovich O., Ambrus R., Szűts A., Aigner Z., Protocols for amorphization of crystalline solids through the application of pharmaceutical technological processes, *Eur. J. Pharm. Sci*. 2007, 32, S18.
26. Troullos E. S., Hargreaves K. M., Butler D. P., Dionne R. A., Comparison of nonsteroidal anti-inflammatory drugs, ibuprofen and flurbiprofen, with methylprednisolone and placebo for acute pain, swelling, and trismus, *J. Oral Maxil. Surg*. 1999, 48, 945-952.

Manuscript received: January 15th 2013